

**REMARKS**

Claims 1-24 and 28-31 are pending in this application. By this Amendment, claims 1-21 are amended and claims 28-31 are added. Non-elected claims 8, 19 and 21-24 have been withdrawn from consideration by the Examiner. Support for the amendments to the claims may be found, for example, in the original claims and in the specification at page 5, lines 30-32 and page 10, lines 9-15. No new matter is added. In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

**I. Claim Objection**

The Office Action objects to claim 9 as being of improper dependent form for failing to further limit the subject matter of a previous claim. By this Amendment, claim 9 is amended to place it in proper dependent form. Accordingly, reconsideration and withdrawal of the objection are respectfully requested.

**II. Rejection Under 35 U.S.C. §112, Second Paragraph**

The Office Action rejects claims 1-7, 9-18 and 20 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. By this Amendment, the claims are amended in light of the Examiner's comments. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

**III. Rejection Under 35 U.S.C. §103**

The Office Action rejects claims 1-7, 9-18 and 20 under 35 U.S.C. §103(a) over WO 98/48783 to Ottoboni et al. (hereinafter "Ottoboni") in view of FR2794763 to Dellacherie et al. (hereinafter "Dellacherie") and U.S. Patent No. 4,904,479 to Illum (hereinafter "Illum"). Applicants respectfully traverse the rejection.

By this Amendment, independent claim 1 is amended to even more clearly distinguish over the applied references. Specifically, independent claim 1 is amended to recite (emphasis added):

A particle in which the core comprises at least one biodegradable organosoluble polymer, characterized in that it is partially or entirely surface-coated with at least one hyaluronan or with one of its derivatives, said hyaluronan being a water-soluble amphiphilic hyaluronan, carboxylic functions of which are in part converted so as to form hydrophobic groups, wherein the hydrophobic groups are anchored in the polymeric core of the particle.

The applied references disclose no such combination of features or otherwise establish any reason or rationale as to why one of ordinary skill in the art at the time of the invention would have modified the teachings of the applied references to arrive at the subject matter of claim 1.

For example, Ottoboni discloses microparticles of the core-shell type having a core that comprises an active substance, a shell that is an inner layer (biodegradable polymer) and an outer layer of a biologically compatible material absorbed on the surface of the inner layer. However, the outer layer is unstable and Ottoboni teaches that a crosslinking agent is added to the mixture to react with the biomaterial envelope and rendering it insoluble, stabilizing the outer wall. See Ottoboni, page 8, lines 21-27; see also Ottoboni, page 6 lines 11-20 (reproduced below for convenience).

An advantage of the inner shell is that it provides additional mechanical or drug delivery properties to the microparticle which are not provided or insufficiently provided by the outer layer, or enhances mechanical properties not sufficiently provided by the outer layer, without being constrained by surface property requirements. For example, a biocompatible outer layer of a cross-linked proteinaceous hydrogel can be physically supported using a high modulus synthetic polymer as the inner layer.

Thus, Ottoboni teaches that the interactions of absorbed molecules are not sufficient to secure the molecules to the surface and a further additive is necessary to ensure the

securing of the molecule relative to the particle, i.e., to avoid the separation of the molecule from the particle. To accomplish this, Ottoboni teaches adding a crosslinking agent, such as glutaraldehyde, to the mixture. See Ottoboni, page 8, lines 21-27. The biological material of the outer layer is then crosslinked to avoid its separation from the inner layer of the particles. Ottoboni does not teach or suggest that "groups are anchored in the polymeric core of the particle," as required by claim 1. Dellacherie does not cure the deficiencies of Ottoboni.

The Office Action acknowledges that Dellacherie does not expressly teach the particle composition as being comprised of the biodegradable organosoluble polymers. Instead, Dellacherie discloses polymers derived from hyaluronic acid for preparing hydrogels, these polymers being obtained by esterification of the carboxylic groups of hyaluronan with hydrophobic aliphatic chains.

Dellacherie also discloses that it is possible to enhance the formation of intramolecular network between the hyaluronan molecules by adding to the mixture a proteins solution. See Dellacherie, page 1, lines 15-19 (page 1, fourth paragraph of the translation). The proteins are similar to a crosslinking agent because it serves to strengthen a network composed of hyaluronan molecules. Thus, similar to Ottoboni, Dellacherie would suggest to one of ordinary skill in the art that a crosslinking agent (proteins) is necessary to ensure the securing of the molecules to each other. Such a crosslinking agent is not a "water-soluble amphiphilic hyaluronan, carboxylic functions of which are in part converted so as to form hydrophobic groups, wherein the hydrophobic groups are anchored in the polymeric core of the particle," as required by claim 1 (emphasis added).

Illum does not cure the deficiencies of Ottoboni and Dellacherie. Illum discloses a drug delivery system comprising particles coated with a material that can have both hydrophilic and hydrophobic domains. As acknowledged by the Office Action, Illum does not expressly teach that the hydrophobic groups are specifically attached to the hyaluronan.

See Office Action, page 10. Additionally, Illum does not teach the conversion of the carboxylic groups of the hyaluronan so as to form hydrophobic groups that can be anchored into the polymer core, as recited in claim 1.

Instead, Illum disclose that the material is intended to be adsorbed on the particles outer surface. See Illum, column 2, line 21; column 3, line 53; column 4, line 53; and column 5, line 33.

Applicant's respectfully submit that there is a fundamental difference between the anchoring of a molecule in a particle and the adsorption of the molecule on the particle. In the first case, the molecule is more or less engaged in and through the particle core while in the second case, the molecule only extends above the particle (and not inside). In the first case, there is no need of a further additive or reagent to ensure the securing of the molecule relative to the particle because this securing is ensured by the interactions between the molecule and the particle.

Similar to Ottoboni and Dellacherie, displacement of the material on the particle surface in Illum is prevented by an additive or crosslinking agent, here by plasma proteins. See Illum, column 2, line 30. Thus, the applied references teach that there is a need to strengthen the intramolecular network of the material molecules to secure this material on the particle surface.

Furthermore, the crosslinking taught by the applied references obviates the need for anchoring the hydrophobic groups in the polymeric core of the particle. Accordingly, one of ordinary skill in the art would have had no reason or rationale to modify the particle of Ottoboni to anchor hydrophobic groups of a water-soluble amphiphilic hyaluronan in the polymeric core of the particle.

Additionally, this crosslinking further causes a modification of the outer surface properties of the particles that then have a lower or no affinity for the CD44 receptors, while

the functionalization of the particles outer surface according to claim 1 allows a higher affinity to be maintained.

Accordingly, none of the applied references, considered either separately or combined, teach or suggest or establish any reason or rationale to provide "water-soluble amphiphilic hyaluronan, carboxylic functions of which are in part converted so as to form hydrophobic groups, wherein the hydrophobic groups are anchored in the polymeric core of the particle," as required by claim 1 (emphasis added).

Thus, Ottoboni, Dellacherie and Illum, considered either separately or combined, do not teach or suggest each and every element of claim 1 and, thus, also would not have rendered obvious claim 1.

Claims 2-7, 9-18 and 20 variously depend from claim 1 and, thus, also would not have been rendered obvious by Ottoboni, Dellacherie and Illum. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

**IV. New Claims**

By this Amendment, new claims 28-31 are presented. New claims 28-31 depend from claim 1 and, thus, distinguish over the applied references for at least the reasons discussed above with respect to claim 1. Prompt examination and allowance of new claims 28-31 are respectfully requested.

**V. Rejoinder**

Applicants also respectfully request rejoinder of non-elected claims 8, 19, and 21-24. Where restriction was required between independent or distinct products, or between independent or distinct processes, and all claims directed to an elected invention are allowable, any restriction requirement between the elected invention and any nonelected invention that depends from or otherwise requires all the limitations of an allowable claim should be withdrawn. For example, a requirement for restriction should be withdrawn when a

generic claim, linking claim, or subcombination claim is allowable and any previously withdrawn claim depends from or otherwise requires all the limitations thereof. Claims that require all the limitations of an allowable claim will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104.

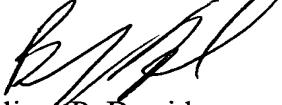
Because the elected product claims are believed to be allowable for at least the reasons presented above, Applicants respectfully request withdrawal of the Restriction Requirement and rejoinder of claims 8, 19, and 21-24.

**VI. Conclusion**

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



William P. Berridge  
Registration No. 30,024

Benjamin S. Prebyl  
Registration No. 60,256

WPB:BSP/jth

Attachments:

Petition for Extension of Time  
Amendment Transmittal

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**OLIFF & BERRIDGE, PLC**  
**P.O. Box 320850**  
**Alexandria, Virginia 22320-4850**  
**Telephone: (703) 836-6400**

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